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low pH of cigarette smoke, nicotine absorption occurs to a significant extent only in the lungs. Conversely, ASAM notes that no important sensory effects are known to result from cigarette smoke in the lungs. Thus, ASAM concludes that “inhalation is the key to nicotine absorption from cigarettes, and there is no reason other than nicotine absorption for the consumer to inhale the smoke.”³⁷²

ASAM further notes that tobacco advertisements historically encouraged consumers to inhale cigarette smoke; according to ASAM, such evidence demonstrates industry intent to ensure adequate nicotine delivery to smokers and thereby achieve substantial pharmacological effects.

FDA agrees that inhalation demonstrates that consumers use cigarettes for substantial pharmacological effects. According to *Gray's Anatomy*, there are no taste or smell receptors below the level of the larynx.³⁷³ No evidence suggests that smokers enjoy any physical sensations associated with smoke in their lungs other than by association with the pharmacological effects of nicotine. Yet smokers learn to inhale—despite such unpleasant reactions as coughing—when the only reason to do so is nicotine absorption.

Indeed, the industry itself has recognized that nicotine absorption is the reason people inhale smoke. In 1982, a leading industry researcher wrote that “[i]t is well known that nicotine can be removed from smoke by the lung and transmitted to the brain within seconds of smoke inhalation. Since it is the major or sole pharmacologically active agent

³⁷² American Society of Addiction Medicine, Comment (Dec. 29, 1995), at 5. See AR (Vol. 528 Ref. 97).

³⁷³ Williams PL, Warwick R, eds., *Gray's Anatomy*, 37th ed. (Philadelphia: WB Saunders, 1989), at 1169-1180. See AR (Vol. 711 Ref. 8).

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in smoke, it must be presumed that this is its preferred method of absorption and *thus why people inhale smoke*.³⁷⁴

2. The smokeless tobacco industry argues that FDA fails to distinguish among different smokeless tobacco products. The comment contends that FDA has based its conclusions entirely on evidence about moist snuff and that this evidence is inapplicable to chewing tobacco.

FDA disagrees that it has ignored the distinction between moist snuff and chewing tobacco or that its evidence applies only to moist snuff. As described in the Jurisdictional Analysis, Benowitz and colleagues found that the rate and amount of nicotine absorption was similar for oral snuff and chewing tobacco in ten healthy volunteers.³⁷⁵ See Jurisdictional Analysis, 60 FR 41572. The total amount of nicotine absorbed from snuff and chewing tobacco was estimated to be 3.6 mg and 4.5 mg, respectively.³⁷⁶ This study confirms that as much or more nicotine is absorbed from each of these products as from cigarettes.

Additionally, in a study submitted by the industry, Walsh and colleagues reported on the use of smokeless tobacco in 1,300 U.S. college athletes.³⁷⁷ Of those surveyed who

³⁷⁴ Letter from Ayres CI (BATCO) to Kohnhorst EE (Brown & Williamson), transmitting partial summary of issues presented at Montebello Research Conference in 1982, at BW-W2-03949 (emphasis added). See AR (Vol. 34 Ref. 584-1).

³⁷⁵ Benowitz NL, Porchet H, Sheiner L, *et al.*, Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum, *Clinical Pharmacology and Therapeutics* 1988;44:23-28. See AR (Vol. 12 Ref. 134-1).

³⁷⁶ *Id.*

³⁷⁷ Walsh MM, Hilton JF, Ernster VL, Masouredis CM, Grady DG, Prevalence, patterns, and correlates of spit tobacco use in a college athlete population, *Addictive Behavior* 1994;19:411-427. See AR (Vol. 526 Ref. 95, appendix VIII).

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used smokeless tobacco, 39% reported using snuff only, 41% reported using both snuff and chewing tobacco, and 16% reported using chewing tobacco only. (Four percent failed to indicate the type of smokeless tobacco used.) Athletes who used both snuff and chewing tobacco generally reported patterns of use that were similar to those of athletes who used snuff only. This study supports similar patterns of use in both snuff and chewing tobacco users and demonstrates use of either moist snuff or chewing tobacco for similar pharmacological effects, such as relieving stress, satisfying strong cravings, and relieving the discomfort of withdrawal.

Thus the use, effects, and nicotine absorption from chewing tobacco compare with moist snuff and cigarettes. *See also* section II.D., below.

b. Comments on Tobacco Use To Satisfy Addiction

1. The tobacco industry argues that FDA's claim in the Jurisdictional Analysis that 75% to 90% of smokers consume cigarettes to satisfy addiction is factually unsupported. The industry contends that FDA selectively extracted pieces of data from various studies to support this rate of nicotine dependence and that the studies FDA relied upon were conducted in sample populations of patients of substance abuse clinics who would have higher "scales of dependence" than the general population.

FDA disagrees. The Agency did not selectively choose studies or selectively extract data from the studies on which it relied to support the reported rates of nicotine dependence. Rather, FDA chose from the published literature those studies that met the following criteria: the study used a definition of addiction established internationally by major public health organizations, the study was capable of estimating the prevalence of nicotine addiction in a well-defined population, and the study used appropriate research

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methods, such as random sampling of a well-defined population, to estimate the prevalence of nicotine addiction. No study relied on surveying smokers at tobacco cessation clinics.

The four studies identified by FDA as satisfying the stated selection criteria for determining the population prevalence of nicotine addiction utilize two data sets and smoking populations. These sample populations represent a generalizable spectrum of smokers.

One of these populations (utilized in a study by Hughes *et al.*)³⁷⁸ included otherwise healthy, non-drug-abusing patients representative of a well-defined population. This was not a selectively extracted population, nor did it have an elevated prevalence of nicotine addiction, as argued by the tobacco industry. It consisted of over 1,000 middle-aged smokers randomly sampled from a well-defined population of male heads of households, who were otherwise representative of men of that age. The men entered the study by identifying themselves as smokers. These men, on average about 51.1 years of age, were estimated to have a lifetime prevalence of nicotine addiction of 90%. The authors report that smoking habits of the men in this study were similar to those reported in previous studies of middle-aged men.

The tobacco industry contests these data on the grounds that: (1) the subjects are representative of the heaviest 22% of U.S. smokers; and (2) the authors at the time argued that the DSM criteria for nicotine addiction were too expansive. The industry's first point is based on a statistical misinterpretation. The industry argues that since the average

³⁷⁸ Hughes JR, Gust SW, Pechacek TF, Prevalence of tobacco dependence and withdrawal, *American Journal of Psychiatry* 1987;144(2):205-208. See AR (Vol. 81 Ref. 292).

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cigarette consumption in the study was 28 cigarettes per day, and because 22% of smokers in 1991 consumed over 25 cigarettes per day, then the study applies to “at most, 22 percent of smokers.” But this reasoning confuses average and median consumption. The heaviest 22% of smokers, on average, consume far more than 25 or 28 cigarettes per day. For example, in 1985, almost half of the smokers in the group who smoked more than 21 cigarettes per day reported smoking 40 or more cigarettes a day.³⁷⁹ Thus, the average number of cigarettes smoked by heavy smokers is well above 28 per day. Accordingly, the smokers represented in the Hughes study smoke less, on average, than “the heaviest” smokers identified by the comment.

The industry’s second argument concerning the authors’ view of the DSM criteria is irrelevant. Although the researchers were initially surprised at the high rates of dependence revealed in this study, the DSM criteria have retained credibility and are widely accepted by clinicians for diagnosing substance dependence.

The second sample of data (utilized in studies by Woody *et al.*, Cottler, and Hale *et al.*)³⁸⁰ is derived from a population studied during the Substance Abuse Disorders Field Trials for DSM-IV. This sample population came from five sites around the United States

³⁷⁹ Department of Health and Human Services, Public Health Service, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, *Reducing the Health Consequences of Smoking—25 Years of Progress, a Report of the Surgeon General* (Atlanta: 1989), at 295. See AR (Vol. 130 Ref. 1593).

³⁸⁰ Woody GE, Cottler LB, Cacciola J, Severity of dependence: data from the DSM-IV field trials, *Addiction* 1993;88:1573-1579. See AR (Vol. 13 Ref. 150).

Cottler L, Comparing DSM-III-R and ICD-10 substance use disorders, *Addiction* 1993;88:689-696. See AR (Vol. 13 Ref. 149).

Hale KL, Hughes JR, Oliveto AH, Helzer JE, Higgins ST, Bickel WK, Cottler LB, Nicotine dependence in a population-based sample, in *Problems of Drug Dependence, 1992*, NIDA Research Monograph 132, (Washington DC: Government Printing Office, 1993). See AR (Vol. 39 Ref. 60).

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and ranged in age from 18 to 44 years. Some of the subjects were from the general population, and others were selected, by a random digit dialing method, from subjects treated for substance abuse. Three separate analyses, using different assumptions and methods, were performed on these data, and the estimates of nicotine dependence reported in three published articles ranged from 77% to 92%. There is no evidence that these rates of nicotine dependence in these sample populations are greater than those for a nonpredisposed population that smoked for the same period. Indeed, the population of non-drug-abusing middle-aged men studied by Hughes *et al.* had a rate of nicotine dependence that was consistent with, and even higher than, the rates found in the Woody *et al.*, Cottler, and Hale *et al.* studies.

One study of nicotine addiction rates cannot be used to establish the prevalence of nicotine addiction because the population examined was not representative of the spectrum of smokers. The sample population in this study by Breslau *et al.* consisted of 394 smokers 21 to 30 years of age who were randomly selected from a well-defined population in a health maintenance organization (HMO).³⁸¹ The median age was 26 years, and 51% of the smokers were addicted to nicotine. These studies reflect that rates of dependence on nicotine increase substantially with duration of exposure and with the smoker's age: Although 51% of these young smokers were dependent on nicotine, fully 90% of the middle-aged smokers in the study by Hughes *et al.* were dependent on nicotine. Moreover, Breslau *et al.* acknowledge that the rate of dependence found in this sample of young smokers may not be representative of the rate among all smokers.

³⁸¹ Breslau N, Kilbey MM, Andreski MA, Nicotine dependence, major depression, and anxiety in young adults, *Archives of General Psychiatry* 1991;48:1069-1074. See AR (Vol. 37 Ref. 17).

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In conclusion, the studies relied on by FDA were not chosen in a preferentially selected manner, but on the basis of study design and methodological considerations. The data sets reflect populations that can be considered representative of cross sections of the U.S. smoking population. There is no evidence to suggest that these studies are not generalizable to the population of smokers. FDA believes that these studies support the claim that 75% to 90% of smokers consume cigarettes to satisfy nicotine addiction. Comments of the American Psychiatric Association agree with this assessment, stating that "DSM based studies . . . found that 80%-90% of adult smokers are nicotine dependent."³⁸²

2. The tobacco industry argues that dependence can never be measured in a large population. This contention is disproved by the successful population-based studies just described. The industry's comments were premised on selective quotations from researchers, none of whom were actually agreeing with the assertion that all such studies are impossible or invalid.

3. The tobacco industry criticizes the data collection methods in the population studies FDA relied upon to support tobacco dependence rates. The industry argues that self-reporting results in inaccurate conclusions and cites an article by Kozlowski *et al.* to support this contention.³⁸³

FDA disagrees. This method of data collection is a scientifically recognized and accepted mode of inquiry for prevalence studies and is relied upon to determine the

³⁸² American Psychiatric Association, Comment (Jan. 2, 1996), at 2. See AR (Vol. 700 Ref. 1020).

³⁸³ Kozlowski LT, Herman CP, Frecker RC, What researchers make of what cigarette smokers say: filtering smokers' hot air, *Lancet* 1980;1(8170):699-700. See AR (Vol. 535 Ref. 96, vol. III.I).

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population prevalence of other disorders, including alcohol dependence, cocaine dependence, and depression.³⁸⁴ Some of these are disorders for which, compared to tobacco use, interview methods would be less likely to reveal accurate results because of the criminal consequences associated with illicit drug use. Moreover, agencies that have expertise in tracking the prevalence of disease in this country, such as the Centers for Disease Control and Prevention, rely on such studies.³⁸⁵ The tobacco industry itself cites multiple surveys based on self-reporting in its comments.

The industry also mischaracterizes the article by Kozlowski *et al.* The article does not support the industry's argument that all self-reported data in population studies are inaccurate. In the article, the authors suggest that self-reports of abstinence among people quitting smoking may be inflated. The authors do not suggest that any other information obtained by self-reporting is unreliable, nor do they give any reason to extrapolate their observations to reporting of other information about smoking behavior. Finally, despite their belief that some smokers may exaggerate the number and success of their attempts at abstinence, the authors never doubt that a large proportion of smokers try to quit.

Accordingly, FDA concludes that the methods used in the population prevalence studies are accepted and reliable.

³⁸⁴ American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 175-272. See AR (Vol. 535 Ref. 96, vol. III.B).

³⁸⁵ See, e.g., Centers for Disease Control and Prevention, Reasons for tobacco use and symptoms of nicotine withdrawal among adolescents and young adult tobacco users—United States, 1993, *Morbidity and Mortality Weekly Report* 1994;43(41):745-750. See AR (Vol. 43 Ref. 162).

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c. Comments on Tobacco Use for Effects on Mood and Weight

1. The tobacco industry contends that FDA has not established that consumers use cigarettes or smokeless tobacco nearly exclusively either to affect mood or to control weight. According to the comment, the studies cited by FDA do not show that a high percentage of consumers use tobacco to affect mood or control weight and that there are an insufficient number of such studies upon which to base a conclusion.

This comment misinterprets the standard for establishing that a product is “intended to affect the structure or any function of the body” through consumer use. As noted in section II.B.1., above, some courts have suggested that where the Agency relies solely on consumer use to establish intended use, consumers must use the product predominantly or nearly exclusively for pharmacological purposes. These cases contain no requirement, however, that consumers use the product in question nearly exclusively for *each* individual pharmacological effect the product produces. Thus, there is no requirement that consumers use nicotine nearly exclusively for each of its pharmacological effects. It is sufficient to establish that consumers as a group use tobacco to obtain any of the several effects on structure or function sought by consumers (for example, to satisfy addiction, for other psychoactive effects, and to control weight). *See ASH v. Harris*, 655 F.2d at 240; *NNFA v. Mathews*, 557 F.2d at 334-336.

FDA also disagrees that there are insufficient studies to support the conclusion that consumers use tobacco to affect mood and control weight. The many studies cited by FDA conclusively show that the majority of tobacco consumers rely on tobacco products to achieve a relaxing or calming effect. *See Jurisdictional Analysis*, 60 FR 41579-41580.

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For example, one survey found that over 60% of smokers aged 16 to 44 believe that smoking reduces nervous irritation.³⁸⁶

The use of cigarettes for weight control is similarly established in numerous studies. These studies show that smokers believe that smoking keeps weight down and that weight control is a significant motivation to continue smoking. The Surgeon General's 1988 Report on Nicotine Addiction reviewed a large number of studies demonstrating that weight control is a powerful motivator for initiation and maintenance of smoking in as many as one-third to one-half of young smokers.³⁸⁷

d. Comments on Nonpharmacological Factors Associated with Tobacco Use

1. The tobacco industry quotes several addiction experts stating that there are social, emotional, and behavioral variables that explain patterns of tobacco use. The industry concludes that consumers do not use tobacco products "nearly exclusively" for the pharmacological effects of nicotine.

FDA disagrees. The industry confuses the details of tobacco use with the reason for use. While multiple factors may explain why a particular person decides to smoke a particular cigarette at a particular moment, data support only one reason why the vast majority of consumers use tobacco products day after day, year after year: to obtain the drug effects of nicotine.

³⁸⁶ McKennell AC, Smoking motivation factors, *British Journal of Social and Clinical Psychology* 1970;49(1):8-22. See AR (Vol. 13 Ref. 152-1).

³⁸⁷ Surgeon General's Report, 1988, at 438-439. See AR (Vol. 129 Ref. 1592).